Ethical Issues in Genetics Research

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Overview

- **Describe the range of genetics research: from bench to bedside**
- **Summarize morally relevant distinctions between information gained from genetics research vs. other kinds of medical research**
- **Explore ethical considerations in different kinds of genetics research**
  - **Reproductive genetics research**
  - **Diagnostic genetics research**
  - **Behavioral genetics research**

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Range of Genetics Research Involving Humans

- **Finding genes related to diseases, traits, behaviors**
- **Finding treatments to compensate for gene dysfunction or replace dysfunctional genes (inherited or acquired mutations) – gene therapy**
- **Identifying individuals (forensic uses)**
- **Examining population differences**
- **Evaluating services, policies**

Types of Genetics Research

- **Basic science research (cloning of a gene, developing a genetic test or conducting animal studies of gene therapy)**
- **Population-Based epidemiologic research (gene-environment interaction studies)**
- **Clinical (applied) research involving genetic testing or gene therapy**

Purpose of Test

- **Diagnostic testing in symptomatic person**
- **Predictive testing**
  - **Presymptomatic test in asymptomatic individual**
  - **Predisposition/susceptibility test**
  - **Pharmacogenomic test**
- **Newborn screening**
- **Reproductive genetic testing**
  - **Carrier testing**
  - **Prenatal testing**
  - **Preimplantation genetic testing (PGD)**

Purpose/Type of Genetic Test

- **Diagnostic:**
  - **Confirms presence of disease in a symptomatic person**
- **Predictive:**
  - ***Presymptomatic:*** **looks for a (highly penetrant, single gene) disease prior to the onset of overt clinical symptoms**
  - ***Predisposition/susceptibility*****: identifies individuals at increased risk of developing a (multifactorial) disease**
  - ***Carrier*****: identifies individuals at risk of passing on a disease-related allele to their offspring**
  - ***Pharmacogenomic*****: identifies genetic variations that influence responses to drugs**

Type of Population Participating in Research Involving Genetic Screening/Testing

- **Adults before conception – carrier screening, PGD**
- **Pregnant women - MSMS, CVS, amniocentesis, carrier screening**
- **Newborns - PKU**
- **Children, adolescents and adults - susceptibility testing for adult-onset disease**

Clinical Validity of the Test

- **Sensitivity – probability that the test will be positive in people with the disease**
- **Specificity – probability that the test will be negative in people without the disease**
- **Positive Predictive Value – probability that people with positive test results will get the disease**

Clinical Utility of Results – Availability/Efficacy of Interventions

- **Do interventions exist?**
- **If so, how effective are they?**
- **If effective, how available/accessible are they?**
- **How good are the data about the availability/efficacy of interventions**

Collateral Implications

- **Potential for psychological distress**
- **Implications for reproductive decisions**
- **Implications for life planning decisions**
- **Implications for other family members**
  - **Relationships with other family members**
  - **Misattributed parentage**
- **Potential for employment/insurance problems**
- **Implications for other conditions in the proband (pleiotropy)**

IRB Considerations

- **What is the nature of the disease being studied?**
- **What is the likelihood that knowing results of the research will harm or benefit an individual?**
- **What is the availability of effective treatment or prevention for the disorder?**
- **What is the burden of such treatment?**

Morally Relevant Characteristics of Different Types of Clinical Genetics Research

	Carrier (CF)	Prenatal (Downs)	Newborn (PKU)	Susceptibility (Hemachromatosis)
Burden of the Disease				
Vulnerability of the Population				
Penetrance of mutation				
Clinical Validity of Test				
Clinical Utility - Is there an effective intervention?				
Collateral Implications				
Acceptability				

(How) Is Genetic Information Different from other Scientific Information?

- **It affects entire families - Frequently involves recruitment of relatives**
- **It is laden with symbolic meaning**
- **Highly probabilistic, complex and emotionally powerful**
  - **interpretation of results depends on mode of inheritance**
  - **creates a new classification of "at-risk" patient – risk of future disease**
  - **possible disclosure of non-paternity**
- **It can influence reproductive decision-making**
- **Primary risks and benefits are psychological and social rather than physical.**
- **Specimens containing DNA can be used to find other genes, or for forensic purposes.**

Does Genetic Research Involving Humans Pose Special Risks?

- **No single line of genetic research poses uniquely special risks**
- **Each of the ethical challenges raised by genetic research apply to other types of research**
- **Taken together--and in light of public expectations and fears—genetic research has caused special concern**
- **Specimens that have been collected for other types of research can be used for genetic research**

Preimplantation Genetic Diagnosis

Is it morally acceptable for researchers to develop technologies that assist parents in "designing" their babies by selecting or altering an embryo they wish to bring to term?

Case #1

Mrs. Jones is a carrier of Duchenne muscular dystrophy (DMD), a progressive, neuromuscular disease from which boys usually die by their mid-twenties. Mrs. Jones had 3 brothers who died of DMD. DMD is an X-linked disorder which means that the gene is passed down only from mothers to sons. Mrs. Jones and her husband want to have a child but they want to make sure they do not have a son with DMD. One morning over coffee, the couple sees the following ad:

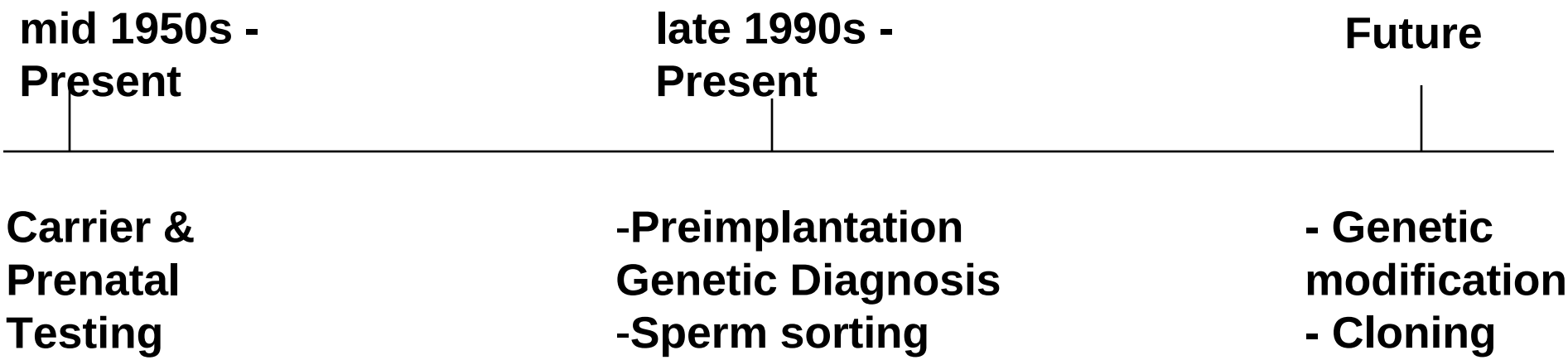
Case #1 continued

"An FDA-sponsored multi-center clinical trial is being launched to study the safety and efficacy of a new technology for sex selection. Based on evidence of success from recent animal studies, this technology has been approved for study in humans. Anyone interested in selecting the gender of their next child can participate in this study. Please call…."

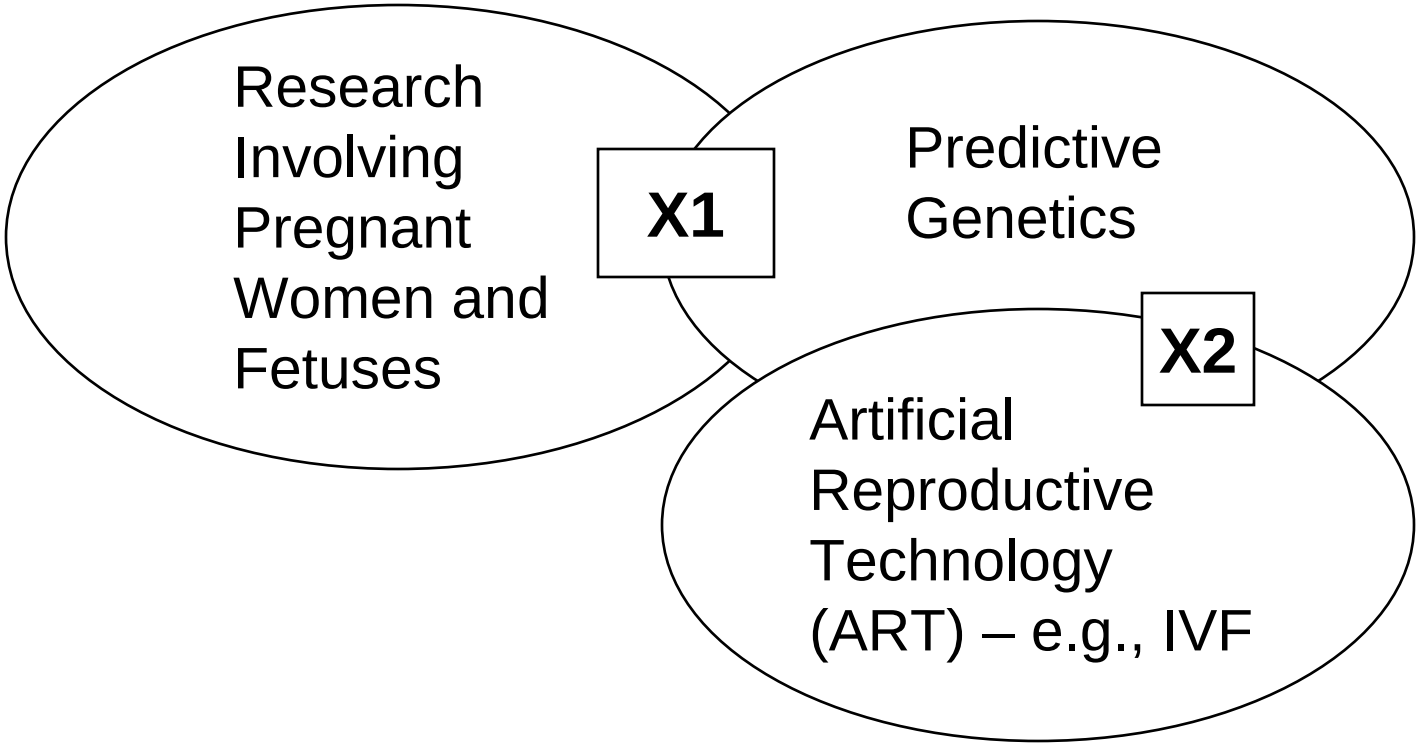
Case #2

Mrs. Smith is 35 years old and very anxious to become a mother. However, she has had 3 miscarriages and her doctors suspect that a fetal abnormality called aneuploidy is responsible for these pregnancy losses. She is referred to a multi-center study designed to assess the use of pre-implantation genetic diagnosis (PGD) to screen out embryos with this genetic abnormality.

Reproductive Genetic Technologies Timeline



Intersection of Ethically Controversial Issues



X1 = genetic research involving pregnant women and fetuses
X2 = genetic research involving the creation or manipulation of embryos outside the womb

Ethical Issues Raised by In Vitro Genetic Testing Technologies

- **Do not explicitly involve questions about abortion**
- **Shift the target population from pregnant women and fetuses to “pre-pregnant” women and embryos.**
- **Can be used not only for the prevention of genetic disease but for genetic enhancement and trait selection**

What is the purpose/goal of the research?

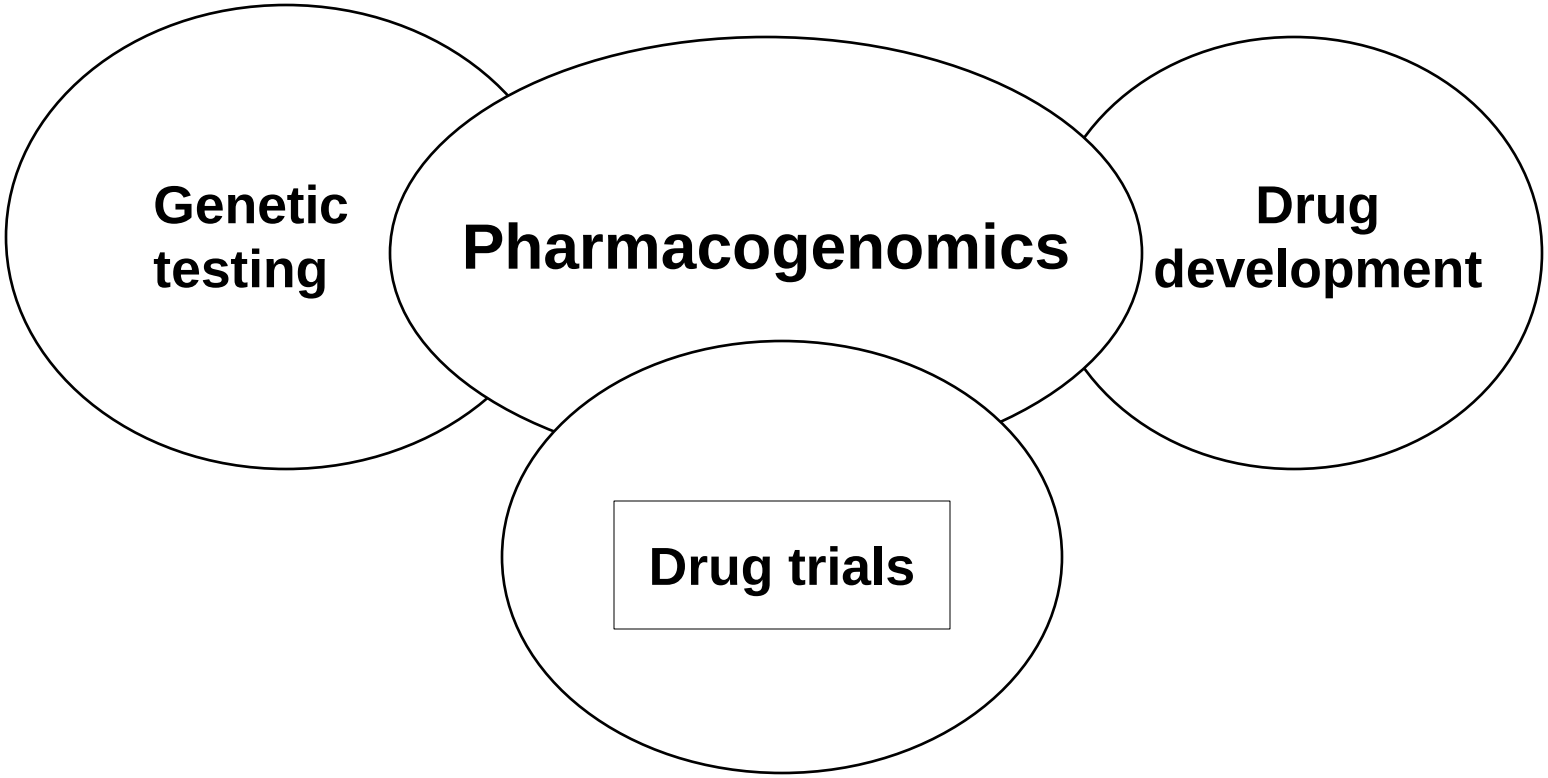
- **Select the sex of a baby**
- **Screen embryos for aneuploidy**
- **Screen embryos for high-risk diseases**
- **Pick an embryo for its specific traits**
- **Genetic manipulation for therapeutic reasons**
- **Genetic manipulation for cosmetic reasons**

Assessment of Risks and Benefits

- **Clinical Utility**
- **Collateral Implications**
  - **Physical**
  - **Psychological**
  - **Social**
  - **Economic**

Genetic Diagnostic Research

- **Range of technologies designed to determine an individual's genotype**
- **Pharmacogenomics - the study of common genetic variations or polymorphisms between individuals and how these variations influence responses to drugs**
- **Genetic testing - detects mutations that either cause relatively rare single gene diseases or increase one's susceptibility to complex disorders**


Genetic testing
Pharmacogenomics
Drug development
Drug trials

Drug Trial

A clinical trial is being launched in which individuals with various risk factors for premature cardiovascular disease (CVD) will undergo DNA genotyping to determine whether they carry a mutation that increases their risk of developing CVD. Then, based on their genotype, they would be assigned to different types of statin drugs.

Potential Benefits of Pharmacogenomics

- **“Individualize” patient care by selecting medications and dosages that are optimal for patients**
  - **Most effective**
  - **Fewest side effects**
- **Reclassify human illnesses using a molecular taxonomy**
  - **Better methods of prevention and early detection**
  - **Reduce stigma**
- **Decrease adverse drug reactions and the costs associated with treating them**

Psychosocial Risks of Pharmacogenomics Research

- **New classifications of conditions that are sub-clinical or “hidden”**
- **Subjects who are found not to respond favorably to a particular drug may be labeled as “non-responders”**
- **Stigmatization and discrimination**

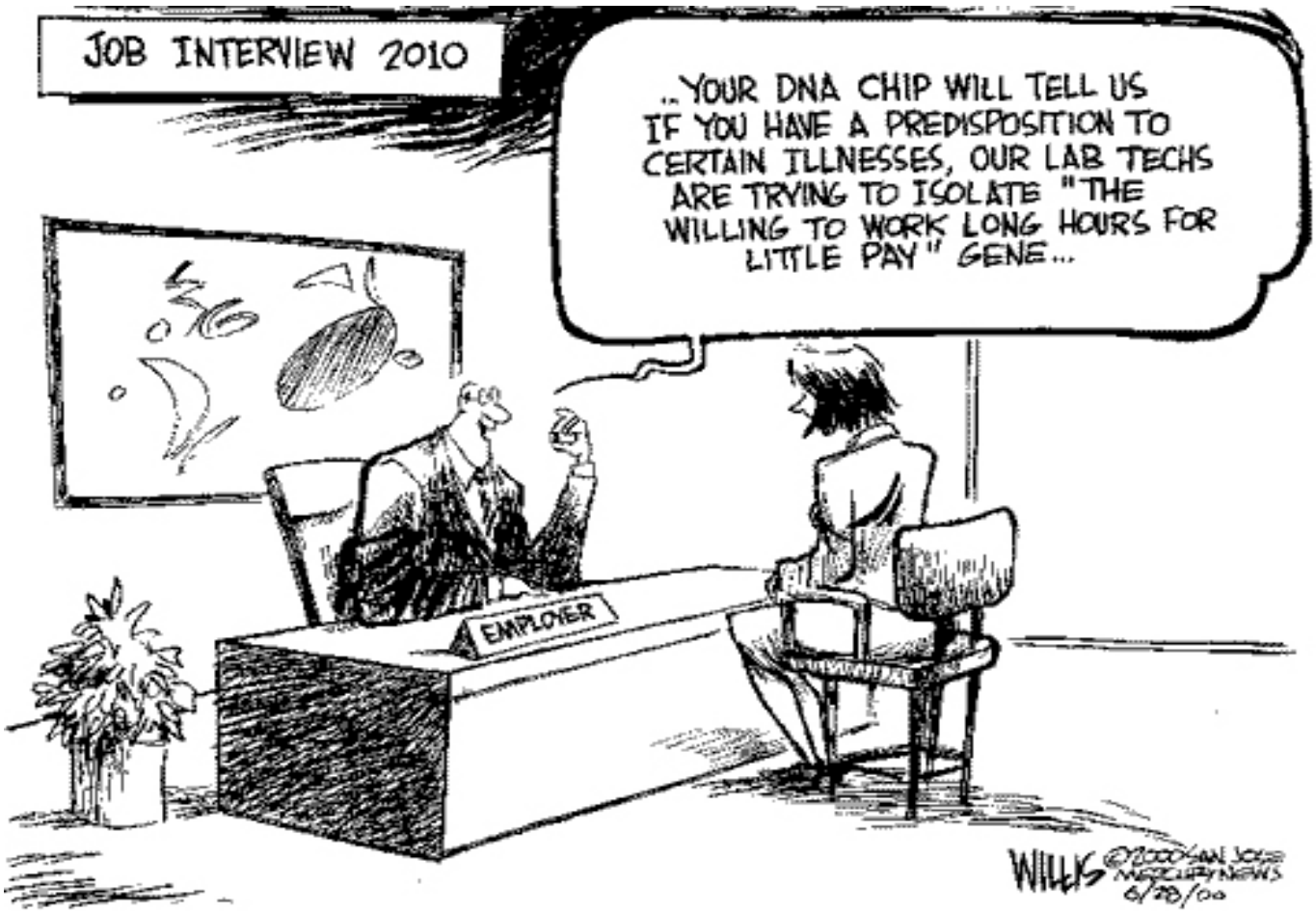
Ethical Challenges Raised by Economic Forces

- **Targeted drug development**
  - **Focus on “responders”**
  - **Could lead to orphan populations**
- **Intellectual property**
  - **Should gene sequences be patented?**
  - **Impeding the sharing of genetic information**

Strategies to Minimize Harms of Pharmacogenomics Research

- **Develop guidelines to address the social challenges of population and individual stratification.**
- **Conduct studies of cost-effectiveness to guide policy decisions**

Research on Genetic Testing for Susceptibility to Complex Disorders and Behaviors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..YOUR DNA CHIP WILL TELL US IF YOU HAVE A PREDISPOSITION TO CERTAIN ILLNESSES, OUR LAB TECHS ARE TRYING TO ISOLATE "THE WILLING TO WORK LONG HOURS FOR LITTLE PAY" GENE...
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MANKIND IS ENTRUSTED WITH THE PLANET EARTH
ooops!
BUT WE LET IT SLIP INTO POLLUTION...
SPLAT!
MANKIND IS ENTRUSTED WITH THE ANIMAL KINGDOM...
ooops
CLONK!
BUT WE THREATEN IT WITH EXTINCTION
NOW THAT WE ARE ENTRUSTED WITH OUR OWN GENETIC MAP...
LET'S HOPE SCIENTISTS LOCATE THE SCREW-UP GENE REALLY QUICKLY...
...ER WHY?

Complex Traits/Behaviors

- **Personality**
- **Fear**
- **Memory**
- **Violence**
- **Sexuality**
- **Intelligence**
- ***Addiction***
- **Obesity**

Potential Ethical Implications

- **Medicalizing behaviors and traits**
- **Stigmatizing behaviors and traits**
- **Changing notions of responsibility and accountability with implications for criminal justice and civil liberties**

Are we ready for….?

A clinical trial involving

….pharmacogenomic testing

….to select the most appropriate smoking cessation/prevention approach

Are we ready for….?

A clinical trial involving

….pharmacogenomic testing

….to select the most appropriate smoking cessation/prevention approach

…..in adolescents??

Susceptibility test for addictive behavior

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This will allow you to know if there is a genetic predisposition tov
addictions. The Reward product line is then available to treat the
towards RDS.

Imagene is an at home genetic testing kit that is simple to use. Here are the actual instructions.

1. Take Foam tipped applicator and rub the inside of left cheek 25 times. Repeat with second applicator.
2. Take foam tipped applicator and rub inside of right cheek 25 times.
3. Take applicator and place inside circle of the indicator card.
4. Press and hold for 1 minute.
5. Flip and reverse Applicator and repeat step 3 within the same circle of the indicator card.
6. The pink circle turns white when the test is complete

"Are you concerned about your children's future? Does your child have the genetic trait that leads to disruptive and addictive personalities? DNA testing can help you to understand and manage a child's behavior before it gets out of control."

What do we know about the science of genetics and smoking?

- **Genes in the serotonin pathway – linked to:**
  - **the likelihood of smoking initiation**
  - **the age at which smoking begins**
- **Genes in the dopamine reward pathway - linked to the ability to quit, including nicotine addiction**
- **Genetic variants interact with psychological and social factors**
- **Pleiotropy – the same genes are implicated in:**
  - **other addictions (cocaine, alcohol)**
  - **many behavioral/psychiatric conditions**
- **There may be racial/ethnic variation in the frequencies of relevant variants/polymorphisms**

Clinical Research Scenarios

- **Test adolescent non-smokers to identify those at-risk of initiation and randomize mutation carriers to a targeted preventive intervention**
- **Test adolescent smokers to identify pharmacogenetic information and target smoking cessation interventions**

Question

Should children and adolescents be involved in (or even the targets of) research on susceptibility to complex diseases/traits?

Morally Relevant Characteristics of Genetic Susceptibility Tests in Children/Adolescents

	FAP	Breast Cancer	Obesity	Smoking-Related Behaviors
Does disease/trait occur in adolescence?	**Yes**	**No**	**Yes**	**Yes**
Prevalence/Severity	**Lo/Hi**	**Lo/Hi**	**High/High**	**High/High**
Penetrance of mutation?	**High**	**High-Mod.**	**Low**	**Low**
Clinical Validity of the Test	**High**	**Mod-High**	**Low**	**Low**
Is there an effective preventive intervention?	**Yes**	**Unknown or risky**	**Exists but ? efficacy**	**Exists but ? efficacy**
Variable prevalence of genotype?	**No**	**Higher in Ashkenazim**	**Higher in Native Amer**	**Higher in African-Amer?**

Justifications for Including Adolescents in Research on Smoking and Genetics

- **Targeting adolescents for smoking prevention studies is an efficient, strategic use of public resources and has the greatest potential to reduce the public health burden of smoking**
- **Adolescents are unique in certain ways and results of studies conducted on adults are not necessarily applicable or generalizable to children**

Justifications for Excluding Adolescents from Research on Smoking and Genetics

- **When there is insufficient information about the likelihood or magnitude of medical and social risks associated with the disclosure of genetic information to participants, research should initially be conducted in adults.**
- **Children/adolescents have a limited ability to provide informed consent due to their cognitive and emotional development, level of autonomy and dependence on family influence.**

Questionable Benefit

- **<u>Clinical validity</u> – there is limited understanding of the genes associated with smoking-related behaviors or the health consequences of smoking**
- **<u>Clinical utility</u> – relaying information about one's genetic predisposition rarely leads to significant behavior change (even when the association between predisposition and disease is strong)**
  - **Alpha 1 antitrypsin deficiency and emphysema**

Potential Risks

- **Pleiotropy - Genetic information about susceptibility to substance abuse and psychiatric disorders may be far more stigmatizing to individuals than information about susceptibility to smoking**
- **“Labeling” adolescents as being at-risk for addiction or for health consequences of smoking may be particularly damaging to their self-image and perceived ability to shape their future.**
- **Create a false sense of security among adolescents who are told that their genotype is associated with reduced likelihood of addiction or adverse health outcome if they smoke**

Challenges to Informed Consent in the Context of Smoking & Genetics

- **Disclosure and understanding of clinical validity, clinical utility, and complex information such as pleiotropy and racial differences**
- **Potential for coercion, particularly among vulnerable subgroups such as adolescents and racial minorities**

Challenges to Informed Consent in the Next Wave of Genetic Research on Smoking

- **What impact, if any, would each of the following have on prospective participants' decisions to enroll in this research?**
  - **Low penetrance of the risk alleles**
  - **Uncertainty about**
    - **whether knowing one's genotype will inhibit smoking behavior**
    - **the efficacy of preventive interventions**
    - **the likelihood of stigma or discrimination**
- **How should information about variation in frequency of risk alleles across socially identified populations be handled in the informed consent process?**

Summary of Ethical Considerations in Genetics Research

- **Purpose/goal of the research**
- **Population being studied**
- **Risks and benefits to participants**
  - **Clinical validity**
  - **Clinical utility**
  - **Collateral implications**
- **Informed Consent**
- **Impact of research on social values, clinical practice and health policy**

Balancing Genetics Research

Benefits to Society and Subjects

Risks of Harms to Subjects and Communities

Protections

- **Study Design**
- **Informed Consent**
- **IRB Review and Consultation**